CHAPTER 1

Introduction

1.1 General background

The need for cleaner chemical processes in industry is obvious. Chemical transformations, which produce in addition to the desired product large amounts of byproducts and waste, are less desirable. Selective transformations using catalytic processes eliminate the requirement of stoichiometric auxiliary reagents in many current processes and can eventually help to decrease the amounts of waste.

In pharmaceutical and agrochemical industries the need for selective transformations is even larger since delicate bioactive compounds are often not robust enough to stand the conditions used in bulk chemistry. Moreover, pharmaceuticals and agrochemicals have to be enantiomerically pure if they contain stereogenic centers. The use of enantioselective catalytic processes can improve the efficiency of the production of finechemicals and pharmaceuticals.

The major part of this thesis describes our efforts to establish a new catalytic system that is capable of achieving epoxidation of olefins with high (enantio)selectivity and using H_2O_2 as oxidant. We focussed mainly on manganese complexes since they are known to accomplish epoxidation of olefins with high enantioselectivity under mild conditions. Although various other metal complexes, including rhenium, tungsten and titanium complexes (see § 1.3), are known to be capable of catalyzing epoxidation reactions, the best results in the catalytic enantioselective epoxidation reactions of unfunctionalized olefins are obtained with manganese complexes. Furthermore, nature provides ample evidence that manganese complexes are attractive redox active systems[1] since in many of metallo-enzymes, manganese is part of the active center. The redox activity of manganese complexes is a requirement for oxidation activity. Examples of redox active manganese enzymes in nature are the oxygen evolving complex superoxide dismutase, catalase and lipoxygenase.[1]

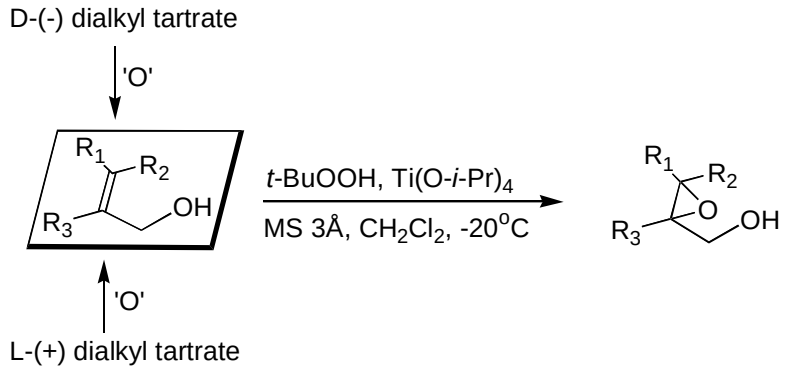
The aim of this chapter is not to give a complete survey of the catalytic oxidation of olefins but to give a summary of the developments achieved in the last decades. An overview will be presented including the most prominent and synthetically applicable catalytic oxidation reactions for the preparation of functionalized organic compounds from olefins.

1.2 Catalytic (asymmetric) functionalization of olefins

Alkenes are versatile building blocks in the (enantio)selective production of organic compounds as will be described in the following paragraphs. The double bond is a handle for a variety of reactions. The prochiral nature of numerous olefins makes is it possible to create in a single reaction an enantiomerically or diastereomerically enriched compound.

1.2.1 Sharpless epoxidation

Allylic alcohols can be converted in a single reaction into the corresponding epoxide with high stereoselectivity. The efficient procedure for the epoxidation of allylic alcohols was developed by Sharpless et al.[2] The catalyst is a complex prepared from titanium-*iso*-propoxide and an enantiomerically pure tartaric acid ester. In general 5-10 % of the titanium-alkoxide is necessary and 10-20 % excess of the tartrate with respect to titanium-*iso*-propoxide. Molecular sieves are required when performing this reaction catalytically. Since both enantiomers of the tartaric acid derivative are readily available, both enantiomers of the desired epoxide can be obtained with high enantiomeric excess. The catalyst employs the hydroxyl function of the allylic alcohol as a handle to accomplish the high enantioselectivity. Most functionalities, except the strongly coordinating protic ones are compatible with this reaction. *t*-Butyl hydroperoxide is used as the oxidant and is converted into *t*-butanol. A variety of allylic alcohols can be epoxidized using this catalyst and enantiomeric excesses usually exceed 90 % and yields are generally above 80%.



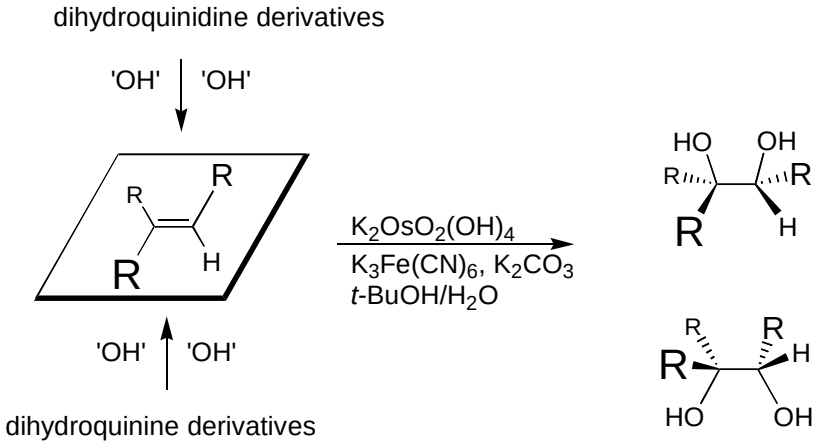
Scheme 1.1 *The Sharpless epoxidation of allylic alcohols*

This reaction is used industrially on a modest scale by Sipsy to produce optically active glycidol. This was only possible after the oxidant had been changed to cumyl hydroperoxide for safety reasons.[3]

1.2.2 Dihydroxylation and aminohydroxylation

Olefins can be employed to prepare diols in a single oxidation reaction. The use of OsO_4[4] or alkaline $KMnO_4$[5] to accomplish this reaction has been known for many years. Due to the toxicity and cost of OsO_4 a catalytic version of this reaction is preferred.[6] Last decade an asymmetric version of this reaction has been developed.[7] The chiral catalytic system consists of an osmium source, a quinine or quinidine derivative as the chiral ligand, an oxidant, which can be either an amine oxide or $K_3Fe(CN)_6/K_2CO_3$ and *t*-butanol/water as the solvent. The chiral quinidine and quinine derivatives produce the opposite enantiomers of the diols. Mixtures of the solid components of the catalytic systems are commercially available. In general, the yields of this reaction are 70 % or higher. The enantioselectivity is usually

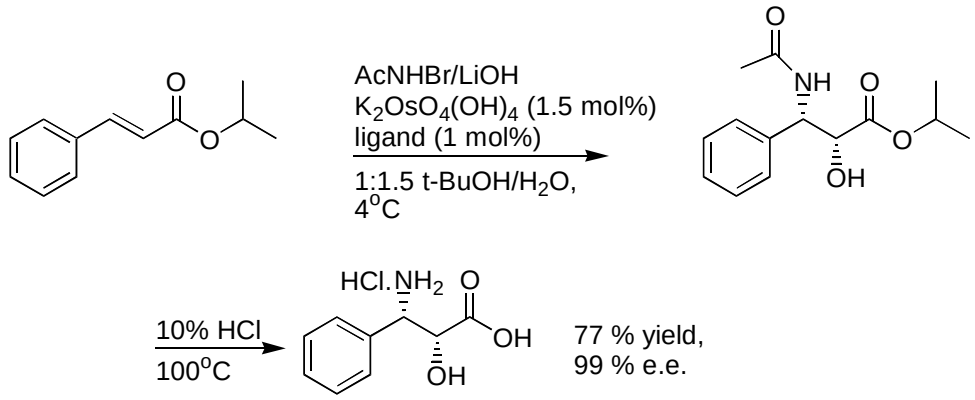
above 75 % and often above 90 %. The absolute configurations can be predicted quite accurately.



Scheme 1.2 *Asymmetric dihydroxylation (size of 'R' indicates the relative size of the substituents)*

Only recently has the asymmetric dihydroxylation been fully optimized by careful examination of pH. Dioxygen can also be used as the oxidant.[8] In this reaction both oxygen atoms of dioxygen are used for the dihydroxylation. Various substrates were converted to the corresponding diols, which were isolated in 51% - 97% yield. The reported enantioselectivies (54% - 96%) were good and only slightly lower than the values reported for the reaction with $K_3Fe(CN)_6/K_2CO_3$ used as oxidant.[9]

By modification the reaction conditions the same catalytic system is able to convert olefins in a single reaction into the corresponding chiral aminoalcohols,[10] which is an important class of compounds used as pharmaceuticals and as chiral auxiliaries and ligands in asymmetric synthesis. The nitrogen source in this reaction is a chloramine salt derived from a sulfonamide, carbamate or amide. The hydroxyl group comes from water. The sense of facial selectivity of both the asymmetric dihydroxylation and aminohydroxylation is the same. The regioselectivity of the reaction has to be carefully tuned by choosing the ligand, solvent and nitrogen source properly.



Scheme 1.3 *Synthesis of 3-phenylisoserine via asymmetric aminohydroxylation*

The reactions have achieved the stage of synthetic applicability and have been used in the total synthesis of a variety of natural products.[7] The asymmetric aminohydroxylation has for instance been used in the synthesis of 3-phenylisoserine (Scheme 1.3), which is a key

compound in the synthesis of the Taxol C13 side chain. *Trans*-propylcinnamate was converted in the corresponding N-acyl aminoalcohol, which was deacylated with HCl and 3-phenylisoserine was obtained in 77% overall yield with excellent enantiomeric excess (99%). The dihydroxylation and aminohydroxylation reaction are not applied industrially.

1.3 Epoxidation of unfunctionalized olefins

Epoxides are an important and very versatile class of organic compounds. The chemistry of epoxides is particularly attractive since various functionalized compounds can easily be prepared from them.[11]

1.3.1 Oxidants

Epoxidation of alkenes can be achieved by a variety of oxidants. These include perbenzoic acids, which are among the most widely used reagents for this purpose in the laboratory,[12] dioxiranes,[13] alkylhydroperoxides, hydrogen peroxide,[12] bleach,[14] iodosylbenzene[14] and molecular oxygen.[12] Most of them suffer from the disadvantage that besides oxygenated products stoichiometric amounts of waste products are formed which have to be separated from the epoxides.

Molecular oxygen, is the most attractive oxidant and used on large scale in industry.[15] Besides the direct conversion of alkenes to the olefins, many epoxides are produced via the corresponding halohydrins.[15] Molecular oxygen does not react with alkenes spontaneously but has to be activated with a suitable catalyst. For instance, in the case of the industrial conversion of ethene to ethylene oxide, one oxygen atom is transferred by a silver catalyst to ethene to form the desired product. The other oxygen atom cannot produce more of the epoxide but it oxidizes ethylene to CO and water. This process is only applicable with alkenes without α-hydrogen atoms present. Propene is converted to the epoxide with the aid of percarboxylic acids or alkylhydroperoxides. The hydroperoxides or percarboxylic acids are produced from, for instance, isobutane or ethylbenzene in a reaction by autooxidation with molecular oxygen. In this process, secondary oxidation products arise from the hydroperoxides or percarboxylic acids as only one oxygen atom is transferred to the olefin to form the epoxide and the other one is left in stoichiometric ‘waste products’. The ‘waste products’ are converted into a variety of industrially important products like acetic acid and styrene.

Epoxidation of olefins in the laboratory is usually accomplished with peracids. *Meta*-chloroperbenzoic acid is most commonly used as the oxidant and most olefins react readily with this compound to give the desired epoxide in good yields. Alternatives for MCPBA include various peracids with higher or lesser reactivity.[12] MCPBA is not safe for use on industrial scale.

Bleach is a very cheap and easy to use oxidant but suffers from the facts that stoichiometric amounts of salt are formed during reactions and the oxidant is highly diluted. Also the basicity of the reaction medium (pH > 10) can be a problem.

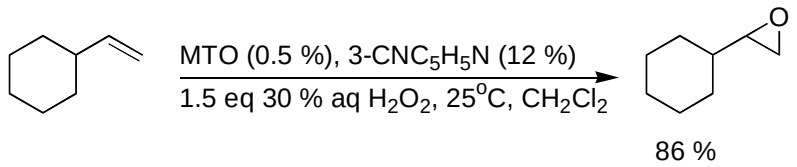
The oxidant of choice is hydrogen peroxide, which can be handled easily and leaves only water as the byproduct. Separation of water from the products is almost never a problem. Hydrogen peroxide, however, is often partially destroyed by catalase type activity,[16,17] a common side-reaction caused by several epoxidation catalysts. In this reaction, two molecules of H_2O_2 are converted into two molecules of water and molecular oxygen.

Scheme 1.4 *The catalase reaction*

1.3.2 Rhenium catalyzed epoxidations

Methyltrioxorhenium (MTO) was found an outstanding epoxidation catalyst using H_2O_2 as oxidant.[18] The acid catalyzed ringopening of the epoxide was however found to be a severe problem and in some cases, the diol was formed quantitatively. The addition of bases was found to suppress this ringopening but the activity of the catalyst diminished using low amounts of bases.

The activity and stability of MTO are enhanced by the addition of excess pyridine to the reaction mixture with respect to the catalyst and also the selectivity of the reaction benefits from the addition of base, suppressing the competing acid catalyzed ringopening of the epoxides.[19] Besides the desired epoxide also a considerable amount of pyridine N-oxide is formed and the reaction has been used to prepare the N-oxides on a preparative scale.[20]

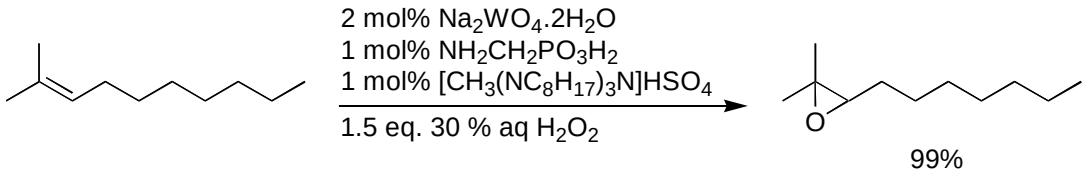


Scheme 1.5 *The MTO catalyzed epoxidation of vinylcyclohexane*

In numerous cases quantitative yields of epoxides can be obtained from styrenes, internal and terminal aliphatic olefins and even tetrasubstituted alkenes. Only 1.5 equivalent of H_2O_2 are necessary and typically 0.5 mol% of MTO is used.

1.3.3 Tungsten catalyzed epoxidations

A salt free method for olefin epoxidation with H_2O_2 has been developed by the group of Noyori.[21] The catalyst in this case is Na_2WO_4 and only 0.2 – 2 mol% of this salt have to be used. Besides the absence of any halogen in this procedure, the preparation of the epoxide is solvent free, which makes it in particular suitable for large-scale processes. Yields in general range from 60 to 80 % for functionalized (alcohols, ketones and esters) alkenes and above 90% for aliphatic alkenes.[22] A highly lipophilic phase-transfer agent such as methyl-trioctylammonium hydrogensulfate is a necessary additive in this reaction as is aminoethylphosponic acid but the role of the latter additive is unclear.



Scheme 1.6 *The tungsten catalyzed epoxidation*

A major disadvantage is the inability to achieve high yields with styrene substrates. The low yields (23 %) obtained for styrene oxide are due to hydrolytic cleavage of the acid-sensitive epoxide and occurs likely at the organic/aqueous interface. More lipophilic styrene derivatives could be epoxidized with higher yields (69 %).

The alcohol functionality of alkenes containing a hydroxyl group are converted in a simultaneous side reaction to carboxylic acid or ketone functionalities. The yield of the epoxidation reaction with such substrates is reduced in this way. This reaction has been optimized and benzylic alcohols and primary alcohols can be oxidized in high yields to the carboxylic acids whereas ketones can be obtained from secondary alcohols generally in yields above 90 %.[23] By using an excess of H_2O_2 cyclohexene can be converted in adipic acid (93% yield),[24] an important industrial product and starting material.[25] However, sofar H_2O_2 is too expensive to be used in a bulk process.

1.3.4 Manganese(III) salen complexes

The first report on the epoxidation of olefins using Mn-salen complexes was published by Kochi et al.[26] Later on, the groups of Jacobsen[27] and Katsuki[28] published at about the same time their first articles on the asymmetric epoxidation using Mn-salen complexes. Since then, epoxidation chemistry using chiral Mn-salen complexes has been expanded and has proven to be a valuable tool in asymmetric synthesis. In general Mn-salen complexes provide the epoxide in yields above 80 % and the e.e. usually exceeds 90 %.

The complexes can be used with a variety of oxidants including bleach,[14] persulfates,[29] MCPBA,[30] periodates,[31] dimethyldioxirane[32] dioxygen and iodosylbenzene.[14] The proposed oxidizing species in this catalytic epoxidation reaction is a Mn(V) oxo intermediate[33] and a catalytic cycle will be discussed in chapter 4. Besides the epoxidation

reaction, an oxidized Mn-salen complex has been used to catalyze Diels-Alder reactions, thereby supplying additional proof for a Lewis-acidic Mn(V) oxo species.[34]

Special conditions make it possible to use H_2O_2 in the epoxidation reaction catalyzed by Mn-salen complexes.[35] Additives like Me-imidazole and carboxylates are used. Although turnover numbers are not as high as with bleach or iodosylbenzene, enantioselectivities ranging from 60 % to 96 % have been reached.

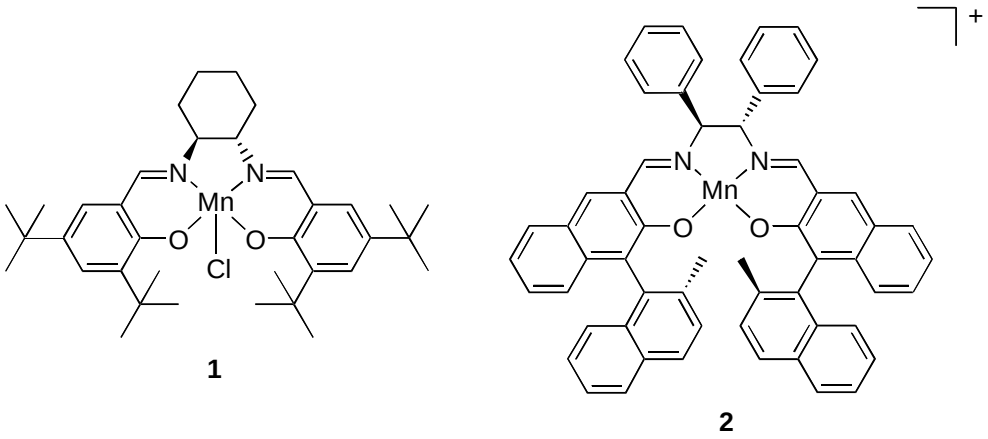
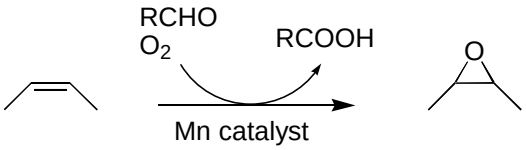


Figure 1.1 *The Mn-complexes used in epoxidation reaction by the groups of Jacobsen and Katsuki*

Best additives with respect to the yield are carboxylate salts.[36] A salen complex with an axial ligand has been synthesized by Berkessel et al.[37] The half-salen system with an intramolecularly linked imidazole was tested with H_2O_2 as terminal oxidant and found to be highly active in the epoxidation reaction of dihydronaphthalene and the corresponding epoxide was obtained in 72 % yield with 64 % e.e. Mn-salen systems are able, without additional ligands, to oxidize sulfides to the corresponding sulfoxide using H_2O_2 as oxidant.[38]

The group of Mukaiyama developed a system that uses dioxygen as oxidant in combination with a reductant. The best reductant proved to be pivaldehyde, which is converted to the corresponding carboxylic acid (Scheme 1.7).[39] The manganese complexes that are used as catalysts are prepared from simple aldimines or ketimines (Figure 1.2). Moderate enantioselectivity has been reached using complex **3** and the enantioselectivity increased with the introduction of more steric bulk in the ester group.[40] Catalyst efficiency however is not high. Dihydronaphthalene epoxide was obtained in 70 % yield with 64 % e.e. using 8 mol% of catalyst. The same catalyst can be used in the aerobic oxidation of sulfides in an enantioselective fashion.[41] Thioanisole was converted in its sulfoxide in 66 % yield with 51 % e.e. using 18 mol% of complex **3**.



Scheme 1.7 *Epoxidation using molecular oxygen*

The O_2/pivaldehyde system was further tested with Mn-salen complexes such as **1**. Rather peculiar is the fact that the face selectivity is different compared to use of oxidants

like iodosylbenzene and bleach.[42] This suggests possible different active species, composed of a chiral catalyst complex, oxygen and reductant. Addition of N-methyl imidazole reverses the face selectivity and the same enantiomers as in the reactions using bleach and iodosylbenzene are obtained.[43] Without addition of N-methyl imidazole dihydronaphthalene is epoxidized in 42 % yield with 12 % e.e. Addition of N-methyl imidazole leads to an increase of the yield to 78 % with 63 % e.e.

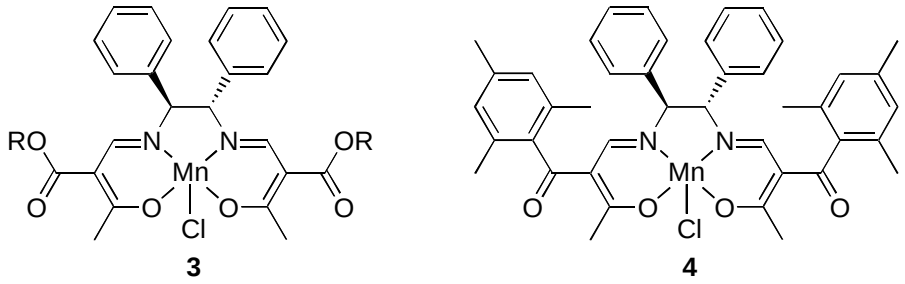


Figure 1.2 *Aldimindinato Mn complexes*

The synthetic applicability of Mn-salen (complex **1**) catalyzed epoxidations is illustrated by the synthesis of N-benzoyl-3-phenylisoserine from *cis*-ethylcinnamate (see for comparison Scheme 1.3).[44] Starting from *cis*-ethylcinnamate the epoxide was obtained with high optical purity. The epoxide was opened regiospecifically with ammonia and in the same reaction the ester fuctionality was converted in an amide which was hydrolyzed to give the carboxylic acid in 33% overall yield. In comparison with the osmium catalyzed asymmetric aminohydroxylation, the reaction provides the key compound, the epoxide, in lower yield due to the concomitant formation of trans-epoxide. This can be explained by a stepwise epoxidation mechanism involving a radical intermediate. The product could however be isolated by crystallization directly from the reaction mixture.

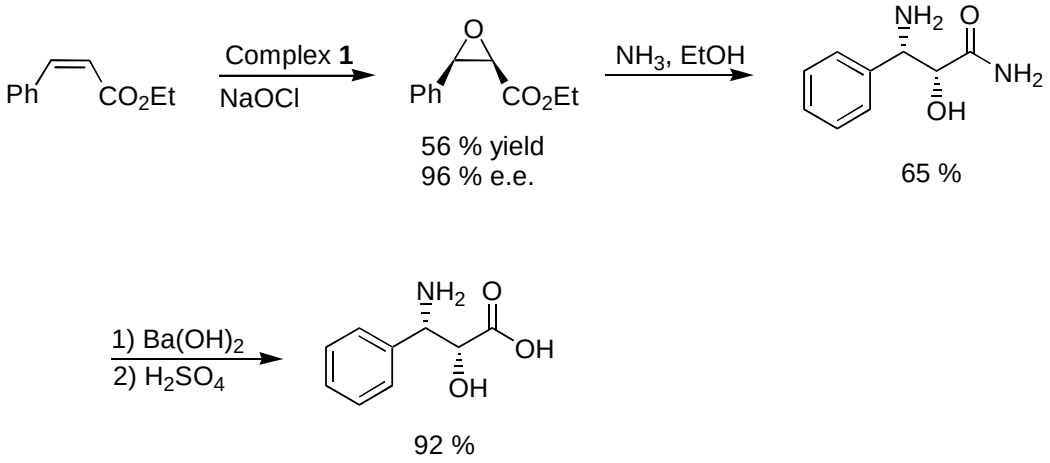


Figure 1.3 *Synthesis of 3-phenylisoserine via asymmetric epoxidation*

1.3.5 Manganese trimethyl-triazacyclononane epoxidation catalysts

The manganese trimethyl-triazacyclononane (Mn-TMTACN) systems (Figure 1.4) were originally developed as bleach catalysts for stain removal by Unilever Research.[45] Besides displaying bleach activity in combination with H_2O_2, the complex was also active as epoxidation catalyst. High turnover numbers (> 400) were reported using styrene as the substrate.[46]

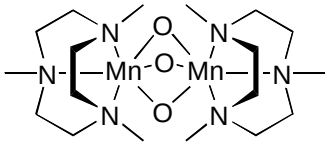


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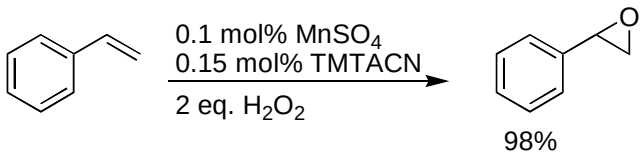
Figure 1.4 *Mn-TMTACN complex*

A severe problem was, however, the high catalase activity of the complex and the large excess of H_2O_2 that had to be used to achieve reasonable yields. The catalase activity can be suppressed by performing the reactions in acetone and the complex can be prepared in situ just before the reaction.[47] The complex is not only active as epoxidation catalyst, but also benzylic alcohols can be oxidized selectively to the corresponding aldehydes with turnover numbers upto 1000.[48]



Scheme 1.8 *The Mn-TMTACN catalyzed epoxidation*

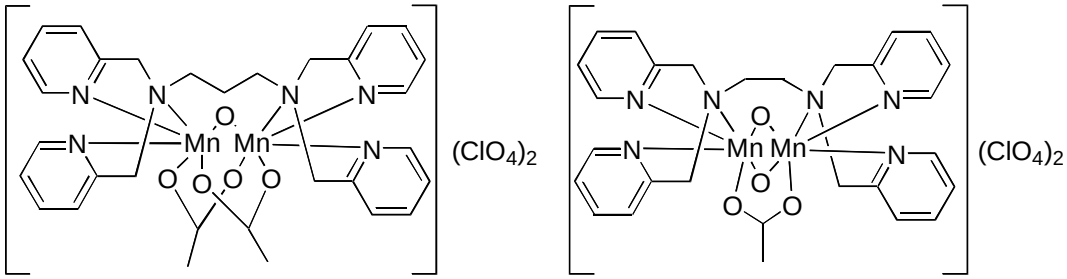
Optically active derivatives of the TMTACN system have already been tested in enantioselective epoxidation of styrenes and chromenes with moderate enantioselectivity.[49] A drawback of this catalyst is the difficult synthesis of functionalized and tailor-made derivatives of the ligand.[50] Fine-tuning of the ligand itself seems not to be a feasible task.

Various successful attempts have been made to improve the catalyst by means of additives. Encapsulation of the complex **4** in zeolites made the system more effective.[51] Addition of oxalate buffers also improved yield and catalyst efficiency but the role of oxalate remains unclear.[52] Even better results were obtained by addition of sodium ascorbate,[53] which is a chiral compound. Catalyst loading of less than 0.1 mol% was reported to be sufficient for a full conversion of methylacrylate to the corresponding epoxide. The addition of chiral additives afforded no enantiomerically enriched products. The Mn-TMTACN system is also able to oxidize secondary alcohols to ketones and primary alcohols to carboxylic acids in yields higher than 90%.[53]

1.3.6 Manganese TPEN epoxidation catalysts

Recently in our group a new catalytic epoxidation system was developed.[54] Isolated and well characterized dinuclear manganese complexes depicted in Scheme 1.9, catalyze the epoxidation with H_2O_2 as terminal oxidant under similar conditions as reported for MnTMTACN complexes. Various alkenes such as styrene, cyclohexene and 2-octene were all converted in their epoxides with good yields. Turnover numbers higher than 300 can be reached easily. As is the case with Mn-TMTACN systems, small structural modifications have large influence on catalyst **6**. For instance shortening the three-carbon spacer to a two-carbon spacer, gives rise to complex **7**, which is totally inactive.[54]

The mechanism of this epoxidation reaction is not known at the present but in the case of the epoxidation of cis-β-methylstyrene a considerable amount of the trans epoxide is found, which is often attributed to radical intermediates.[47,55]



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Scheme 1.9 *Complexes based on TPEN ligands*

1.4 IOP Catalysis

The research described in this thesis has been performed within the IOP Catalysis program. The **I**nnovation **O**riented Research **P**rogram on Catalysis has been initiated by the Netherlands Ministry of Economic Affairs to promote mission oriented research in the field of catalysis, in order to stimulate the collaboration between academia and industry. Mission oriented research lies along the road between fundamental science and novel applicable technologies as is illustrated by the technology S-curve of Figure 1.7. This implies that an IOP research project should have an exploratory character and be based on a vision of its potential applications in industry.

In general, the aims of these projects involve innovation and development of catalytic reactions on an academic level, but with a view towards industrial application of these processes. In the course of the execution of these research projects, there is a continuous dialog between the researcher and the industrial users committee of the specific IOP project.[56]

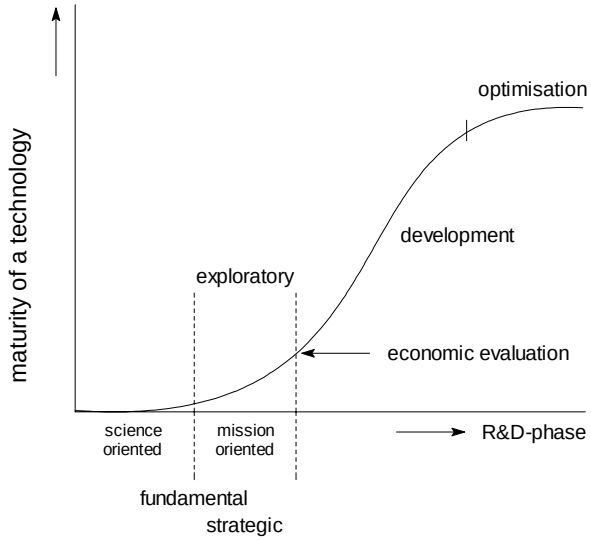

Figure 1.7 *The technology S-curve, showing the relation between maturity of a technology and stage of the desired R&D*

1.5 Aims of this study

The goal of the research described in this thesis is the design and development of new manganese based epoxidation catalysts. The new catalysts should exhibit high selectivity towards epoxide formation from olefins with H_2O_2 as oxidant, circumventing the 'catalase activity'. A second objective has been the modification of the catalyst, in order to achieve enantioselective epoxidation.

The research has concentrated on the development of new ligands stabilizing active species that are capable of oxidizing olefins with H_2O_2 as oxidant. From the tetra- and pentadentate ligands various complexes have been synthesized, characterized and tested in the epoxidation reaction. Furthermore, catalysts in situ prepared from ligands and Mn(II) salts, have been tested in the epoxidation reaction. The most successful ligand in the epoxidation reaction has been modified and various enantiomerically pure analogs were obtained. These ligands were tested in the manganese catalyzed enantioselective epoxidation reaction.

In addition to the research focussed on manganese complexes, a study has been performed on an iron complex, synthesized form a new pentadentate ligand. The complex was well characterized and its catalytic behavior in oxidation reaction with various organic substrates was studied.

The outline of this thesis is given below:

- *Chapter 2* describes the synthesis and characterization of new penta- and tetradentate ligands with phenol, pyridine and amine functionalities.
- *Chapter 3* deals with the synthesis and characterization of new manganese complexes. Several of the newly synthesized ligands form well defined di- and tri-nuclear manganese complexes and the ligands show multiple chelation modes.

- In *Chapter 4* the homogeneous manganese catalyzed epoxidation of unfunctionalized olefins with H_2O_2 as oxidant is described. Both well defined complexes and in situ prepared complexes were studied. We were able to epoxidize styrene with 80 % yield using only 2 equivalents of H_2O_2.
- In *Chapter 5* our attempts to develop an enantioselective catalytic system are described. Several new chiral ligands, based on the achiral ligands that were successfully employed in epoxidation of olefins, were synthesized and tested in the asymmetric epoxidation reaction. We were able to epoxidize alkenes with enantioselectivities upto 20 %.
- In *Chapter 6* a study of a new ligand is shown, which is able to form well defined iron and manganese complexes. The iron complex is able to catalyze the oxidation of various substrates with H_2O_2.

1.6 References

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